B-type natriuretic peptide concentrations predict the progression of nondiabetic chronic kidney disease: the Mild-to-Moderate Kidney Disease Study

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Abstract: BACKGROUND: Plasma concentrations of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are diagnostic and prognostic biomarkers of heart failure and are also increased in patients with chronic kidney disease (CKD). We examined the relevance of BNP and NT-proBNP as predictors of CKD progression. METHODS: Of 227 nondiabetic patients with mild-to-moderate renal insufficiency, 177 patients ages 18-65 years were followed in a prospective multicenter cohort study for a period of < or = 7 years. CKD progression was assessed by recording renal endpoints, defined as doubling of baseline serum creatinine or end-stage renal disease (ESRD) requiring renal replacement therapy. RESULTS: BNP and NT-proBNP were significantly higher among 65 patients who reached the combined renal endpoint than among the 112 who did not [median (interquartile range) 61 (27-98) ng/L vs 39 (20-70) ng/L, P = 0.023, for BNP; 320 (117-745) ng/L vs 84 (44-176) ng/L, P <0.001, for NT-proBNP)]. Each increment of 1 SD in log-transformed BNP and NT-proBNP increased the risk of CKD progression by hazard ratios of 1.38 (95% CI 1.09-1.76, P = 0.009) and 2.28 (1.76-2.95, P <0.001), respectively. After adjustment for other established prognostic factors of CKD progression, NT-proBNP but not BNP remained a significant independent predictor of the combined renal endpoint. CONCLUSIONS: Increased BNP and NT-proBNP concentrations indicate an increased risk for accelerated progression of CKD to ESRD and may prove to be valuable biomarkers for the assessment of prognosis in patients with CKD.

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B-Type Natriuretic Peptide Concentrations Predict the Progression of Nondiabetic Chronic Kidney Disease: The Mild-to-Moderate Kidney Disease Study

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Background: **Plasma concentrations of B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) are diagnostic and prognostic biomarkers of heart failure and are also increased in patients with chronic kidney disease (CKD). We examined the relevance of BNP and NT-proBNP as predictors of CKD progression.**

Methods: **Of 227 nondiabetic patients with mild-to-moderate renal insufficiency, 177 patients ages 18–65 years were followed in a prospective multicenter cohort study for a period of ≤7 years. CKD progression was assessed by recording renal endpoints, defined as doubling of baseline serum creatinine or end-stage renal disease (ESRD) requiring renal replacement therapy.**

Results: **BNP and NT-proBNP were significantly higher among 65 patients who reached the combined renal endpoint than among the 112 who did not [median (interquartile range) 61 (27–98) ng/L vs 39 (20–70) ng/L, $P = 0.023$, for BNP; 320 (117–745) ng/L vs 84 (44–176) ng/L, $P < 0.001$, for NT-proBNP)]. Each increment of 1 SD in log-transformed BNP and NT-proBNP increased the risk of CKD progression by hazard ratios of 1.38 (95% CI 1.09–1.76, $P = 0.009$) and 2.28 (1.76–2.95, $P < 0.001$), respectively. After adjustment for other established prognostic factors of CKD progression, NT-proBNP but not BNP remained a significant independent predictor of the combined renal endpoint.**

Conclusions: **Increased BNP and NT-proBNP concentrations indicate an increased risk for accelerated progression of CKD to ESRD and may prove to be valuable biomarkers for the assessment of prognosis in patients with CKD.**

Chronic kidney disease (CKD),[7] an increasingly prevalent condition in Western societies, is frequently associated with a progressive decrease in glomerular filtration rate (GFR), leading to end-stage renal disease (ESRD), for which renal replacement therapy is required *(1)*. Although this decrease in GFR is fairly constant in the individual patient, there are significant interindividual differences in the rate of decrease. Established risk factors for CKD progression include type of renal disease; nonmodifiable patient characteristics such as ethnic back-

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[7] Nonstandard abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; ESRD, end-stage renal disease; BNP, B-type natriuretic peptide; NT-proBNP, N-terminal proBNP; CHF, congestive heart failure; LVD, left ventricular dysfunction; IQR, interquartile range; BMI, body mass index; RAAS, renin-angiotensin-aldosterone system.

ground, sex, age, and baseline kidney function; and modifiable risk factors including blood pressure, glycemic control in diabetes, degree of proteinuria, serum albumin concentration, smoking, dyslipidemia, and anemia *(2, 3)*.

B-type natriuretic peptide (BNP) and N-terminal proBNP (NT-proBNP) concentrations are associated with the severity and prognosis of congestive heart failure (CHF) and left ventricular dysfunction (LVD) and have emerged as useful biochemical markers for the diagnosis and prognosis of heart diseases *(4–8)*. Plasma concentrations of NT-proBNP and BNP are also increased in patients with impaired kidney function and have been significantly correlated with the estimated GFR in patients with and without CHF *(9–11)*. The mechanisms underlying these associations and correlations are not well understood but are postulated to reflect impaired renal clearance of natriuretic peptides. We hypothesize that increased BNP and NT-proBNP plasma concentrations reflect the homeostatic response of the heart to disturbed renal function in the context of a cardiorenal syndrome, which is suggested to amplify progression of both CHF and CKD *(12)*. We investigated, in a prospective study, whether increased BNP and NT-proBNP concentrations predict the progression of disease in patients with mild or moderate chronic nondiabetic kidney disease.

Patients and Methods

STUDY POPULATION

In 1997, 227 white male or female patients with primary CKD and mild-to-moderate impaired renal function were recruited from 8 nephrology departments in Germany, Austria, and South Tyrol (Italy) *(13, 14)*. Study patients (ages 18–65 years at the time of recruitment) had nondiabetic CKD and had visited the outpatient department at least once during the preceding year. Exclusion criteria were serum creatinine >6 mg/dL (>531 μmol/L); malignancy; liver, thyroid, or infectious disease; nephrotic syndrome (defined as daily proteinuria >3.5 g/1.73 m^2); organ transplantation; immunosuppressive treatment; allergy to ionic contrast media; and pregnancy. All patients were recruited by a single investigator. The study was approved by the institutional ethics committees, and all participants gave their informed consent before inclusion in the study.

Of the primary cohort of 227 patients, 177 could be followed prospectively over a period of ≤84 months. Patients received regular follow-up care in the outpatient ward, and defined endpoints—doubling of baseline serum creatinine or ESRD with the need of renal replacement therapy—were reported to the study coordinating center. Fifty patients (22%) were lost to follow-up because they moved or were not referred by their usual doctors to the study centers. Patients lost to follow-up had significantly better renal function but did not differ significantly in sex or age *(14)*.

BLOOD SAMPLING AND MEASUREMENTS

At baseline, we collected blood samples for the preparation of serum and EDTA plasma in plastic tubes after patients had fasted overnight for ≥12 h. The samples were centrifuged immediately at 1500*g* and 4 °C for 10 min. Aliquots of the supernatants were stored at −80 °C. GFR was assessed by the iohexol method as described *(14, 15)*. In 2004, frozen plasma samples were used to measure BNP and NT-proBNP in the Institute of Clinical Chemistry of the University Hospital Zurich on the AxSYM System (Abbott Laboratories; CV <10% at concentrations of 90 to 2000 ng/L) and the Roche Diagnostics Modular Analytics E170 system (CV <4% at concentrations of 30 to 5000 ng/L). The lower limits of detection are 15 ng/L for the BNP assay and 5 ng/L for the human NT-proBNP assay. For statistical analyses, BNP concentrations below the detection limit (n = 44) were assigned a value of 15 ng/L. All measurements were performed by a single technician who was unaware of the clinical information of the patients.

The clinical laboratories of the local hospitals where the patients were recruited and followed up measured plasma concentrations of creatinine in fresh samples by use of the Jaffe methods of various manufacturers. Although these measurements were not yet fully standardized, they allowed assessment of the endpoint "doubling of creatinine", because each patient was monitored by the same laboratory and each laboratory maintained its method throughout the study period.

STATISTICAL ANALYSIS

Continuous data are presented as median and range or interquartile range (IQR). Discrete data are given as counts and percentages. We compared categorical variables by χ^2 test. We used the Mann–Whitney *U*-test and Kruskal–Wallis analysis for comparisons of continuous data and the nonparametric Jonckheere–Terpstra test for analyzing trends in the relationship between GFR and BNP or NT-proBNP.

Data with skewed distributions [BNP, NT-proBNP, body mass index (BMI), degree of proteinuria, GFR, total cholesterol, HDL-cholesterol, triglycerides, and diastolic and systolic blood pressure] were normalized by natural logarithmic transformation. This procedure decreased the skewness to values close to 0 for all indicated parameters. We used Spearman rank regression analysis to assess correlations of GFR with BNP or NT-proBNP plasma concentrations.

We performed univariate Cox proportional hazards analysis to identify predictors of the combined and isolated renal endpoints. We constructed multivariate Cox proportional hazard models to assess the independent prognostic roles of BNP and NT-proBNP in addition to known confounders of CKD progression (see *Results*). We used ROC analysis to determine optimal cutoff values for the analysis of BNP and NT-proBNP by Kaplan Meier time-to-event analysis. We assessed the equality of sur-

vival distributions by log-rank test. For the analyses that used doubling of baseline serum creatinine as an isolated endpoint, patients who reached ESRD at an earlier time point were excluded. For all tests, $P < 0.05$ was considered to be statistically significant. Data were processed and analyzed with SPSS 12.0.1 software (SPSS).

Results

PATIENTS

The primary causes of CKD were glomerulonephritis (n = 97, 43%), polycystic kidney disease (n = 37, 16%), interstitial nephritis (n = 24, 11%), other types of renal disease (n = 43, 19%), and unknown (n = 26, 12%). Twenty-eight patients had a history of cardiovascular events [myocardial infarction, aortocoronary bypass, percutaneous transluminal coronary angioplasty, angiographically verified stenosis of the coronary arteries, stroke, or a symptomatic stenosis of the peripheral arterial vessels (carotid, aortoiliac, or femoral arteries)].

Baseline clinical characteristics of 227 patients with nondiabetic CKD are shown in Table 1. Patients were classified into 4 groups according to baseline stages of GFR as defined in the clinical practice guidelines of the National Kidney Foundation *(2)*. In addition to expected increases in plasma concentrations of creatinine and urea ($P < 0.001$), decreasing GFR was significantly associated with the need for antihypertensive treatment and increasing protein excretion ($P = 0.004$). Notably, BMI, systolic or diastolic blood pressure, and previous cardiovascular events did not differ significantly between groups.

ASSOCIATION OF BNP AND NT-proBNP PLASMA CONCENTRATIONS WITH RENAL FUNCTION

Baseline BNP and NT-proBNP concentrations were measured in 225 and 222 patients of the study cohort, respectively, and ranged from <15 to 445 ng/L [median (IQR) 41 (20–82) ng/L] and from 7 to 3950 ng/L [105 (43–283) ng/L], respectively. Baseline BNP and NT-proBNP concentrations correlated with GFR (Spearman correlation coefficients $R_s = -0.168$, $P = 0.011$, and $R_s = -0.609$, $P < 0.001$, respectively). Both BNP and NT-proBNP plasma concentrations were progressively higher in patients with

Table 1. Baseline clinical and laboratory data of patients with CKD stratified into 4 groups according to baseline GFR.[a]

Group	GFR ≥90 mL · min^{-1} · (1.73 m^2)$^{-1}$	GFR 60–89 mL · min^{-1} · (1.73 m^2)$^{-1}$	GFR 30–59 mL · min^{-1} · (1.73 m^2)$^{-1}$	GFR <30 mL · min^{-1} · (1.73 m^2)$^{-1}$	All patients
n	72	49	63	43	227
Median age, years (range)	39 (18–64)	49 (19–63)	48 (20–65)	56 (29–65)	48 (18–65)[b]
Sex, n (%)					
Female	22 (31)	15 (31)	19 (30)	17 (40)	73 (32)
Male	50 (69)	34 (69)	44 (70)	26 (60)	154 (68)
Prior cardiovascular events, n (%)	5 (7)	8 (16)	9 (14)	6 (14)	28 (12)
Median BMI, kg/m^2 (IQR)	24.1 (21.6–26.9)	25.4 (23.2–28.2)	25.0 (23.2–27.4)	24.8 (23.2–28.7)	24.6 (22.7–27.4)
Smoking status, n (%)					
Nonsmoker	36 (50)	26 (53)	35 (56)	24 (56)	121 (53)
Former smoker	18 (25)	12 (25)	17 (27)	10 (23)	57 (25)
Current smoker	18 (25)	11 (22)	11 (17)	9 (21)	49 (22)
Median creatinine, μmol/L (IQR)	98 (84–115)	126 (110–150)	193 (150–248)	309 (241–408)	142[b] (1061–210)
Median urea, mmol/L (IQR)	5.32 (3.50–6.96)	6.66 (5.26–8.41)	11.66 (7.49–15.98)	14.07[c] (12.95–20.48)	7.66[b,c] (5.33–13.35)
Median proteinuria, g/24 h (IQR)	0.36 (0.13–0.82)	0.57 (0.16–1.93)	0.80 (0.27–1.83)	0.89 (0.36–1.52)	0.56[d] (0.18–1.42)
Median systolic blood pressure, mmHg (IQR)	130.0 (120.0–141.5)	135.0 (120.0–157.5)	140.0 (123.0–150.0)	140.0 (122.0–152.0)	135.0 (120.0–150.0)
Median diastolic blood pressure, mmHg (IQR)	83.0 (73.0–90.75)	85.0 (80.0–100.0)	90.0 (80.0–99.0)	90.0 (80.0–95.0)	86.0[e] (80.0–95.0)
Antihypertensive medication, n (%)	41 (57)	41 (84)	57 (90)	40 (93)	179 (79)[b]
Lipid-lowering agents, n (%)	10 (14)	11 (22)	18 (29)	6 (14)	45 (20)

[a] GFR was measured by iohexol clearance. To convert values for creatinine to μmol/L, multiply by 88.5. To convert values for urea to mmol/L, multiply by 0.116.
[b] *P* value provided for global comparisons: $P < 0.001$.
[c] Urea value is missing for 1 individual.
[d] *P* value provided for global comparisons: $P < 0.01$.
[e] *P* value provided for global comparisons: $P < 0.05$.

progressively more advanced stages of CKD as defined by the Disease Outcomes Quality Initiative of the National Kidney Foundation *(2)*. As evident from the box-whisker plots in Fig. 1, the increase in NT-proBNP concentrations was more pronounced (medians ranged from 39 ng/L in group 1 to 456 ng/L in group 4, $P < 0.001$ for both Kruskal–Wallis test and Jonckheere–Terpstra test) than the increase of BNP concentrations (medians ranged from 34 ng/L in group 1 to 57 ng/L in group 4; Kruskal Wallis test $P = 0.019$ and Jonckheere–Terpstra test $P = 0.002$ for trend). When BNP concentrations among individual groups were compared, the difference was significant only between groups 1 and 3 ($P = 0.046$) and between groups 1 and 4 ($P = 0.003$). In contrast, NT-proBNP concentrations differed significantly between groups 1 and 2 ($P < 0.001$) and became even more pronounced with a further decrease in renal function. Thus even a moderate decrease of renal function was associated with increased NT-proBNP concentrations.

BNP and NT-proBNP as predictors of CKD progression

Of the 177 patients available for follow-up, 65 reached at least 1 of the predefined renal endpoints: 29 patients progressed to ESRD requiring renal replacement therapy, and 36 patients experienced a doubling of baseline serum creatinine without needing ESRD. BNP and NT-proBNP concentrations were significantly higher among patients who reached both renal endpoints than among those who did not [median (IQR) 61 (27–98) ng/L vs 39 (20–70) ng/L, $P = 0.023$, for BNP; 320 (117–745) ng/L vs 84 (44–176) ng/L, $P < 0.001$, for NT-proBNP]. Patients were stratified into 2 groups by BNP and NT-proBNP concentrations above and below the optimal cutoff concentrations suggested by ROC analysis according to the combined endpoint, namely 56 ng/L for BNP [area under the ROC curve (95% CI) 0.603 (0.515–0.692), $P = 0.025$] and 213 ng/L for NT-proBNP [0.758 (0.681–0.835), $P < 0.001$; Fig. 2]. Patients with BNP above the cutoff had lower GFR than those with BNP below the cutoff (Table 2). A significantly higher proportion of patients with higher BNP concentrations reached both endpoints vs patients with BNP below the cutoff (48.6% vs 28.6%, $P = 0.007$). Compared with patients with NT-proBNP concentrations below the cutoff, those with NT-proBNP concentrations above the cutoff were older and had higher creatinine and urea concentrations, lower GFR, and higher systolic blood pressure (Table 2). Furthermore, a markedly higher proportion of patients with NT-proBNP concentrations above the cutoff reached at least 1 of the predefined renal endpoints (66% vs 19%, $P < 0.001$).

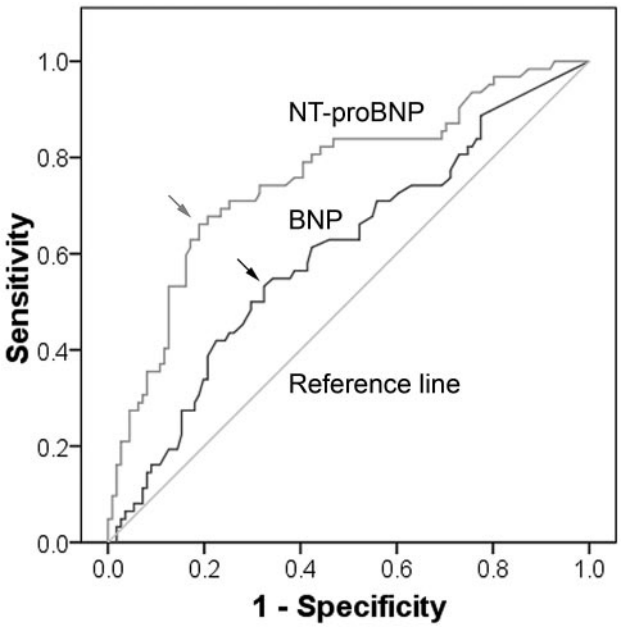

Fig. 2. ROC analysis of BNP and NT-proBNP as predictors of the combined renal endpoint of CKD progression.

Arrows indicate the localization of the optimal cutoff concentrations for BNP (56 ng/L; sensitivity, 0.532; specificity, 0.676) and NT-proBNP (213 ng/L; sensitivity, 0.661; specificity, 0.811).

Kaplan–Meier analysis was performed to compare the strata of BNP or NT-proBNP concentrations for the time to reach 1 or both endpoints (Fig. 3). The corresponding log-rank test revealed a significant difference for both parameters with respect to combined endpoints ($P = 0.003$ for BNP and $P < 0.001$ for NT-proBNP). The unadjusted hazard ratios (95% CI) for the combined renal

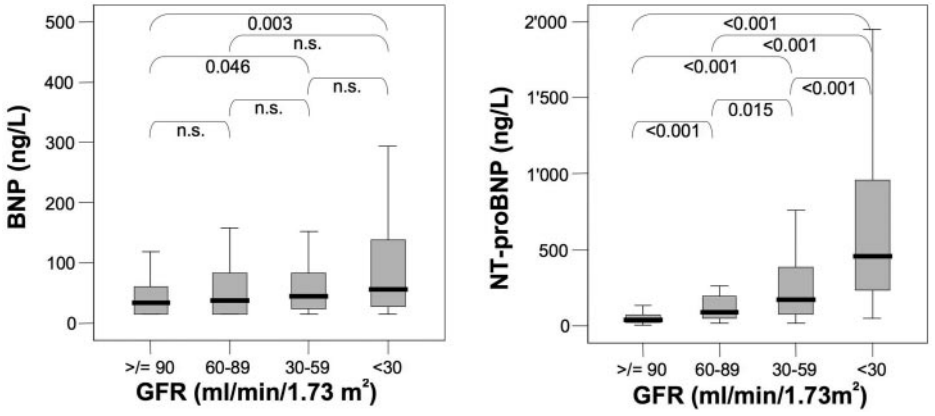

Fig. 1. Plasma concentrations of BNP and NT-proBNP in relation to CKD stages (Disease Outcomes Quality Initiative of the National Kidney Foundation) based on GFR determined by iohexol clearance.

The *horizontal lines* inside the *box* indicate the respective median, the *box* spans the IQR, and the *whiskers* represent the largest and smallest values that are not outliers. Values given in *brackets* reflect *P* values for differences among individual subgroups.

Table 2. Baseline clinical characteristics according to BNP and NT-proBNP values above and below the cutoff.[a]

	BNP			NT-proBNP		
	≤56 ng/L	>56 ng/L	*P* value	≤213 ng/L	>213 ng/L	*P* value
n	105	70		112	62	
Median age, years (range)	48 (20–64)	51 (18–65)	NS	44.5 (18–64)	54 (23–65)	<0.001
Sex			NS			NS
Female	33 (31)	26 (37)		33 (30)	26 (42)	
Male	72 (69)	44 (63)		79 (70)	36 (58)	
GFR, $mL \cdot min^{-1} \cdot (1.73\ m^2)^{-1}$	62.8 (38.5–92.7)	46.5 (29.0–77.9)	0.032	77.0 (47.1–101.4)	36.6 (19.0–47.2)	<0.001
Creatinine, μmol/L	144 (108–201)	179 (122–290)	NS	124 (102–164)	253 (177–347)	<0.001
Urea, mmol/L	8.74 (5.41–13.4)	9.16 (6.23–14.07)[b]	NS	7.66 (5.16–10.54)	13.49 (7.24–17.95)[b]	<0.001
Proteinuria, g/24 h	0.69 (0.17–1.41)	0.81 (0.31–1.79)	NS	0.56 (0.16–1.37)	1.00 (0.34–1.93)	0.023
Systolic blood pressure, mmHg	134.0 (120.0–150.0)	138.0 (120.0–153.0)	NS	130.0 (120.0–149.25)	140.0 (125.0–157.0)	0.011
Diastolic blood pressure, mmHg	87.0 (80.0–95.0)	86.0 (77.8–95.0)	NS	85.0 (76.25–93.75)	89.0 (80.0–95.25)	NS
CKD stage			NS			<0.001
1	29 (28)	13 (19)		42 (38)	1 (2)	
2	26 (25)	13 (19)		31 (28)	8 (13)	
3	32 (30)	25 (36)		30 (27)	25 (40)	
4	18 (17)	19 (27)		9 (8)	28 (45)	
Both endpoints reached, n (%)	30 (29)	34 (49)	0.007	21 (19)	41 (66)	<0.001

[a] Values for continuous variables are median (IQR) if not otherwise indicated. Discrete data are given as n (%). Cutoffs for BNP (56 ng/L) and NT-proBNP (213 ng/L) were determined by ROC analysis. To convert values for creatinine to mg/dL, divide by 88.4. To convert values for urea to mg/dL, divide by 0.1665.

[b] Urea value is missing for one individual.

outcome by BNP and NT-proBNP above the cutoff were 2.09 (1.27–3.44), $P = 0.004$, for BNP and 5.16 (3.01–8.82), $P < 0.001$, for NT-proBNP. The same was true for the isolated clinical endpoint ESRD: during the follow-up, both BNP and NT-proBNP cutoff values significantly discriminated patients reaching the endpoint from those who did not [log-rank test $P = 0.004$ for BNP and $P < 0.001$ for NT-proBNP; hazard ratio (95% CI) 2.90 (1.37–6.15), $P = 0.005$, for BNP and 9.17 (3.71–22.69), $P < 0.001$, for NT-proBNP above the respective cutoff]. For the isolated endpoint of doubling of serum creatinine, the discriminating power was less pronounced, reaching statistical significance for NT-proBNP but not for BNP [log-rank test $P < 0.001$ for NT-proBNP and $P = 0.11$ for BNP, hazard ratio (95% CI) 4.08 (2.04–8.16), $P < 0.001$, for NT–proBNP and 1.72 (0.88–3.38), $P = 0.12$, for BNP].

The results of the univariate Cox regression analysis for BNP and NT-proBNP were similar when the variables were analyzed as continuous covariates. Both BNP and NT-proBNP were identified as predictors of the combined renal endpoints (Table 3). After stratification for the single endpoints, univariate Cox regression analysis revealed that both BNP and NT-proBNP are associated with upcoming need for renal replacement therapy, whereas only NT-proBNP emerged as a significant predictor of a doubling of creatinine during the follow-up period (Table 3).

In multivariate Cox proportional hazards analysis of the combined renal outcomes (Table 3), adjustment for sex and age led to a slightly increased hazard ratio for NT-proBNP but did not substantially influence the predictive value of BNP. After adjustment for GFR and further covariates known to be related to the progression of CKD (BMI, plasma albumin, hemoglobin, degree of proteinuria, diastolic blood pressure, systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, smoking, use of antihypertensive medication, prior cardiovascular events), the association of NT-proBNP, but not that of BNP, with the combined renal outcome remained significant (hazard ratio 1.91, 95% CI 1.22–3.01, $P = 0.005$, for NT-proBNP). An increase of NT-proBNP by 1 SD nearly doubled the risk of progressing to 1 of the predefined renal endpoints during the follow-up. Adjustment for age and sex exerted a minor effect on the strength of the associations of NT-proBNP with the isolated renal endpoints in multivariate Cox regression analysis but showed no effect for BNP. Further adjustment for traditional risk factors as indicated in the legend of Table 3 identified NT-proBNP, but not BNP, as an independent predictor of both isolated endpoints [hazard ratio (95% CI) 1.90 (1.03–3.49), $P = 0.039$, for the doubling of baseline serum creatinine; 2.32 (1.05–5.14), $P = 0.038$, for ESRF requiring dialysis therapy].

Association of BNP and NT-proBNP with cardiovascular events in the past and during follow-up

Twenty-seven patients with a past cardiovascular event at baseline were more frequently male (16% vs 5%), were

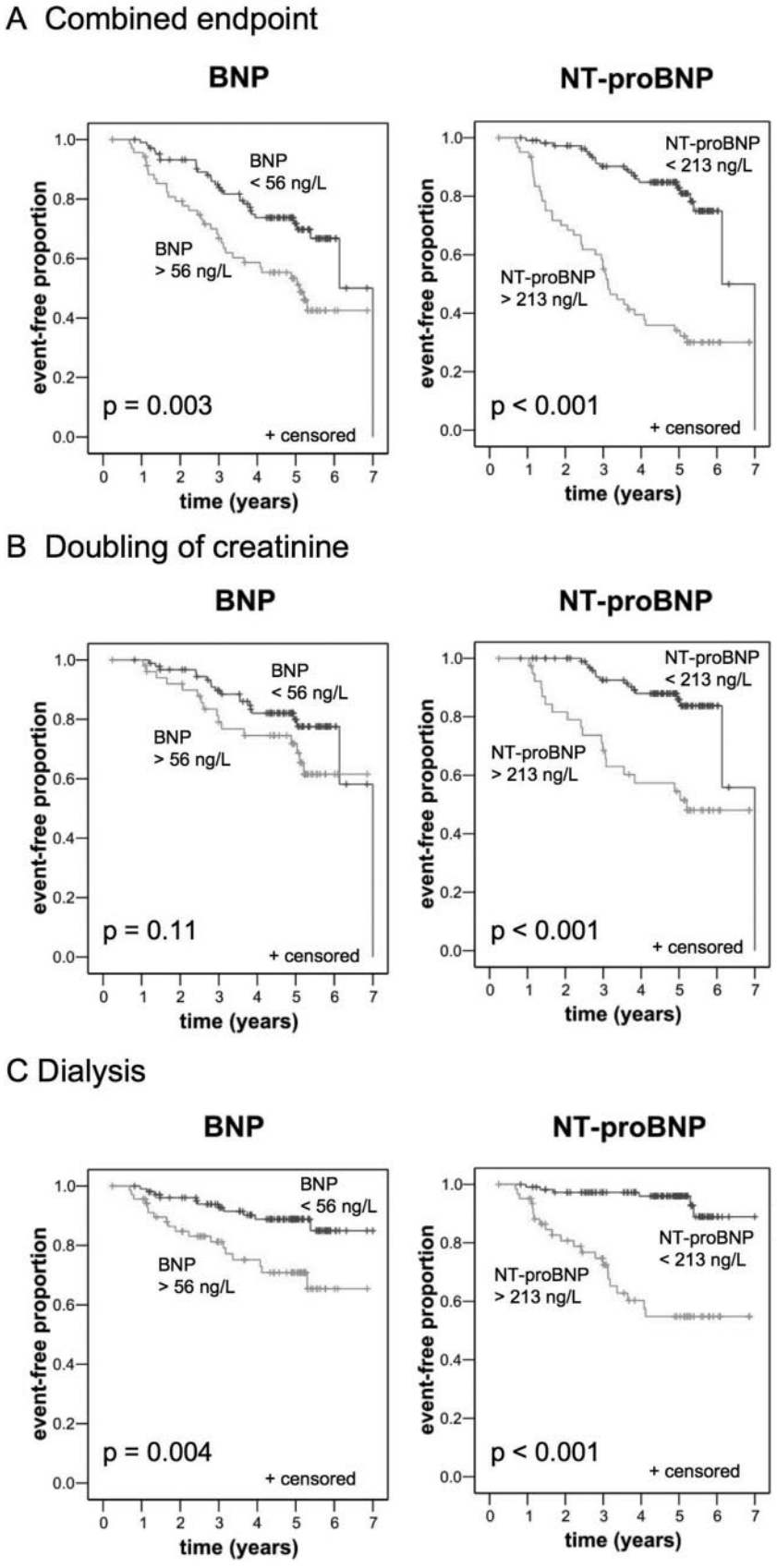

Fig. 3. Kaplan–Meier survival curves of patients with mild or moderate CKD according to BNP and NT-proBNP and different renal endpoints.

Data were stratified according to cutoffs for BNP (56 ng/L) and NT-proBNP (213 ng/L), as well as both (*A*) and single (*B* and *C*) renal endpoints.

Table 3. BNP and NT-proBNP as predictors of renal endpoints.[a]

	Analysis	BNP	NT-proBNP
Both endpoints	Univariate analysis	1.38 (1.09–1.76), 0.009	2.28 (1.76–2.95), <0.001
	Adjusted for sex and age	1.35 (1.06–1.72), 0.015	2.43 (1.82–3.25), <0.001
	Adjusted for further variables[b]	1.19 (0.89–1.59), 0.25	1.91 (1.22–3.01), 0.005
Doubling of creatinine	Univariate analysis	1.23 (0.88–1.73), 0.22	2.01 (1.39–2.91), <0.001
	Adjusted for sex and age	1.23 (0.88–1.72), 0.23	2.27 (1.51–3.41), <0.001
	Adjusted for further variables[b]	1.23 (0.80–1.90), 0.34	1.90 (1.03–3.49), 0.039
Dialysis	Univariate analysis	1.65 (1.16–2.34), 0.006	3.07 (2.09–4.53), <0.001
	Adjusted for sex and age	1.61 (1.12–2.32), 0.010	3.15 (2.03–4.91), <0.001
	Adjusted for further variables[b]	1.22 (0.77–1.93), 0.40	2.32 (1.05–5.14), 0.038

[a] Data are hazard ratio (95% CI), *P* value. Hazard ratios were determined by univariate and multivariate Cox proportional hazard analysis and are indicated for each increment of 1 SD in the log-transformed BNP (1 SD = 0.817) and NT-proBNP (1 SD = 1.304) values, respectively.

[b] Adjusted for sex, age, BMI, plasma albumin, hemoglobin, degree of proteinuria, GFR, diastolic blood pressure, systolic blood pressure, total cholesterol, HDL-cholesterol, triglycerides, smoking, use of antihypertensive medication, and prior cardiovascular events.

older [median (range) 56 (39–62) years vs 47 (18–65) years], and presented with higher NT-proBNP concentrations [median (IQR) 199 (86–549) ng/L vs 91 (39–263) ng/L]. Other factors, including BNP and GFR, did not differ significantly. Ten patients experienced a major cardiovascular event and 3 patients died during the 7 years of follow-up. These numbers were too low to allow calculation of reliable estimates for incident events by Cox regression analysis. Median (range) concentrations of BNP and NT-proBNP in the 10 patients with cardiovascular events were 39 (<15–294) ng/L and 148 (20–3606) ng/L, respectively.

Discussion

We show that BNP and NT-proBNP plasma concentrations are associated with the progression of renal failure in patients with primary, nondiabetic CKD. BNP and NT-proBNP are both released from the heart in response to wall stretch induced by volume or pressure overload and have been introduced into the clinical routine as valuable diagnostic and prognostic markers of CHF and LVD *(4–8, 16)*. In addition, BNP and NT-proBNP plasma concentrations have been found to be increased in patients with impaired renal function *(10, 17)*. In our study, in accordance with published data *(9–11, 16)*, median BNP and NT-proBNP concentrations increased in parallel with decreasing renal function. Hence, even a moderate restriction of GFR was associated with a significant increase of NT-proBNP values.

To date, the increase of BNP and NT-proBNP concentrations in patients with impaired renal function has been considered an unwanted confounder in the diagnostics of CHF. Moreover, the reason for increased BNP and NT-proBNP concentrations in patients with impaired renal function has not been clarified. The most frequently used explanation is renal retention of both BNP and NT-proBNP. In accordance with this explanation are the strong correlations of GFR with BNP and NT-proBNP concentrations. Surprisingly, increased rather than decreased urinary concentrations of BNP have been found in patients with renal impairment compared with healthy controls *(18)*. Furthermore, urinary NT-proBNP was significantly correlated with NT-proBNP and creatinine concentrations in plasma of healthy individuals *(19)*. These inverse correlations between renal function and urinary BNP or NT-proBNP indicate that renal retention is not the only reason for increased plasma concentrations of BNP and NT-proBNP in patients with impaired renal function. Increased concentrations in such patients may arise rather from an increased release of both BNP and NT-proBNP into the circulation.

In the multivariate Cox regression analysis, NT-proBNP but not BNP remained a significant predictor of accelerated progression of CKD to 1 or both endpoints even after adjustment for GFR and further factors associated with progression of CKD. Furthermore, in patients with CKD both estimated GFR and left ventricular mass have been described to be independent confounders of BNP and NT-proBNP concentrations *(20)*. Because BNPs are released from cardiomyocytes, the progressive increase of BNP and NT-proBNP with decreasing renal function may reflect cardiac involvement in CKD patients in terms of a cardiorenal syndrome. Because no other data on cardiac function than BNP and NT-proBNP values are available for our patients, this model remains to be shown by future studies. However, prevalences of LVD and CHF are increased in patients with renal impairment, and the prevalence of renal dysfunction is increased in patients with cardiac dysfunction *(10, 21, 22)*. This coincidence and the correlation of severity of renal impairment with LVD and CHF point to a mutual relationship of renal and cardiac impairment.

Progression of CKD is associated with impaired salt regulation and extracellular fluid volume expansion *(23)*. Therefore, the inverse relationship between GFR and plasma BNP or NT-proBNP concentrations may reflect an increased volume load of the heart as a consequence of volume expansion due to restricted GFR. The increased activity of the renin-angiotensin-aldosterone system (RAAS) in CKD and even in very early, clinically asymp-

tomatic stages of CHF may influence BNP and NT-proBNP plasma concentrations. Because BNP is induced by angiotensin II in cardiac myocytes *(24)* and counteracts the water and sodium retention caused by activated RAAS and suppresses aldosterone *(25)*, increased concentrations of BNP and NT-proBNP in renal failure and their association with poor renal prognosis might reflect the activation of the RAAS, which is supposed to promote CKD. Thus, from a physiological perspective, increased concentrations of either BNP or NT-proBNP in renal failure reflect not only impaired glomerular filtration but also a counterregulatory response of the heart to changes in hemodynamics and water homeostasis. BNP and NT-proBNP may hence be considered markers of the cardiorenal syndrome, a pathophysiological condition that amplifies the progression of both cardiac and renal failure, leading to ESRD and CHF *(12)*. Thus, BNP and NT-proBNP have recently evolved as markers for the diagnosis and prognosis of CHF in CKD patients *(9, 11, 26–28)*. In addition, a small study *(28)* and the present study identified BNP and NT-proBNP as prognostic markers for the progression of CKD.

Our data demonstrate that increased BNP and NT-proBNP concentrations are associated with accelerated progression of mild and moderate primary CKD to renal endpoints. After adjustment for several factors known to be associated with the progression of CKD, however, only NT-proBNP emerged as an independent predictor of one or both renal endpoints. NT-proBNP, therefore, provides prognostic information in addition to the established risk markers of progression of CKD. Although NT-proBNP is not the biologically active peptide, it appears to be the more suitable prognostic measure to estimate the risk of CKD progression compared with active BNP. This may be due to the longer half-life of NT-proBNP compared with BNP (120 vs 22 min) *(29)*, so that NT-proBNP more stably reflects changes in hemodynamics. In addition, the role of BNP as a prognostic biomarker of CKD progression might be compromised because 20% of patients presented with BNP concentrations below the detection limit (NT-proBNP was detectable in all cases); however, the optimal cutoff of 56 ng/mL is well above the detection limit of 15 ng/mL.

Our study has 3 major limitations that must be addressed in further studies. First, because the time of follow-up varied considerably among patients who reached neither of the renal endpoints, our study design is not appropriate to define conclusive cutoffs for stratifying the risk of reaching ESRD within defined time intervals. Future studies involving sequential measurements of BNP and NT-proBNP are needed to define reliable cutoff values. Second, our data are restricted to nondiabetic patients who were only 18–65 years old at the time of inclusion in the study. It will be important to show whether our observations are also valid in older patients and patients with diabetes. Third, we have no data on the structure and function of the heart, either at baseline or during follow-up. These data are needed to unravel whether natriuretic peptides are associated with CKD progression independently of subclinical CHF and whether increased BNP and NT-proBNP reflect structural heart disease or a homeostatic response to water and salt retention as well as activated neurohormonal systems.

In conclusion, increased concentrations of BNP and NT-proBNP indicate an increased risk for accelerated progression of mild or moderate CKD ultimately to ESRD.

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